DOCKET NO: 267336US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HANS-ULRICH PETEREIT, ET AL.	: EXAMINER: WESTERBERG
SERIAL NO: 10/532,831	:
FILED: MARCH 9, 2006	: GROUP ART UNIT: 1618
FOR: MULTILAYER DOSAGE FORMS, WHICH CONTAIN ACTIVE SUBSTANCES AND WHICH COMPRISE A NEUTRAL CORE, AND AN INNER AND OUTER COATING CONSISTING OF METHACRYLATE COPOLYMERS AND METHACRYLATE MONOMERS	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In accordance with 35 U.S.C. § 134, that the claims of the present application have been twice rejected, this brief is submitted in response to the final rejection dated November 4, 2010.

REAL PARTY OF INTEREST

The real party of interest is Roehm GMBH & Co. KG, Darmstadt, Germany.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1-3, 8-11, 13, 14 and 16 are active.

Claims 10 and 11 are withdrawn.

Claims 4-7, 12, and 15 were cancelled.

Claims 1-3, 8, 9, 13, 14 and 16 are rejected and appealed.

The appealed claims are presented in Appendix I.

STATUS OF AMENDMENTS

No outstanding amendments are present in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the pending, rejected and appealed independent claim 1 with reference to exemplary support in the originally filed application is:

1. (rejected) A multilayer dosage form ***[page 4, last line to page 1, line 1]*** comprising

a) a neutral core, ***[page 5, line 3]***

b) an inner methacrylate copolymer coating comprising at least 90% by weight of (meth)acrylate monomers having neutral radicals, wherein the methacrylate copolymer has a minimum film-forming temperature as specified in DIN 53 787 not exceeding 30°C, and a pharmaceutically active substance bound to the methacrylate polymer, ***[page 5, lines 16-22]*** wherein the inner coating does not comprise plasticizer; ***[page 25, line 10]*** and

c) an outer coating which comprises a (meth)acrylate copolymer which is composed of 10 to 30% by weight methyl methacrylate, 50 to 70% by weight methyl acrylate and 5 to 15% by weight methacrylic acid, ***page 20, line 39 to page 21, line 4***.

wherein the values for the percentage release of active substance in a hypotonic and an isotonic release medium based on phosphate buffer pH 6.8 do not differ from one another at any time in the period from 1 to 5 hours by more than 10%. ***[page 25, lines 25-31]***

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The first ground of rejection to be reviewed on appeal is whether Claims 1-3, 8, 9, 13, 14 and 16 are properly rejected under 35 USC 103(a) in view of Ulmius (US 5,643,602) with Beckert *et al* (WO 01/68058).
2. The second ground of rejection to be reviewed on appeal is whether Claims 1-3, 8, 9, 13, 14, and 16 are properly rejected under 35 USC 103(a) in view of Ulmius (US 5,643,602) with Gang *et al* (*Proceedings of the 7th SECJ,* 2001).

ARGUMENT

I. INTRODUCTION

The pending claims in this application are directed to a multilayer dosage form of a pharmaceutical which includes a neutral core, an inner layer composed of a methacrylate polymer which itself is composed of particular (meth)acrylate monomers having particular properties, wherein the inner coating does not comprise plasticizer, a specified outer core, and an active bound to the polymer of the inner core. As discussed in the application in the paragraph bridging pages 5-6, this formulation provided initial slow release (due to the outer layer) followed by a similar slow release of the active that was not affected by the ionic strength of the dissolution medium.

As discussed in the application in the paragraph bridging pages 5-6, this formulation provided initial slow release (due to the outer layer) followed by a similar slow release of the active that was not affected by the ionic strength of the dissolution medium. More specifically, in the Examples of this application it is demonstrated that when a pharmaceutically active substance is bound to the methacrylate polymer of the inner coat, the release was not affected by the ionic coat. In other words, the unexpected effect that is observed in the application is not a function of the outer coating but the inner coating with active bound thereto. The outer coatings modify the start of release as is shown in Example 4 (using Eudragit® FS30D for delivery to the colon) and Example 5 (using Eudragit® L30D for delivery to the intestine).

Starting on page 26, Examples 1-3 embedded budesonide (active) in Eudragit® NE 30D (the inner coat methacrylate polymer). As explained in the application on page 31, FIG. 2 shows the comparative release profiles of Example 1 in isotonic and hypotonic conditions. Example 1 has no outer coating.

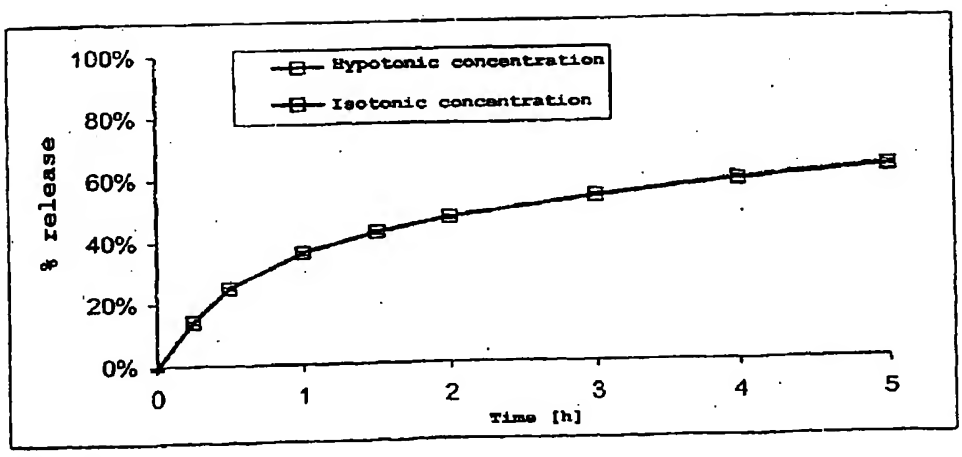

Fig. 2

Example 5, adds the outer coating of Eudragit L30D-55 as a gastroresistant coating. As explained on page 33, FIG. 5 shows the comparative release profile of the formulation with Eudragit® NE30D with budenoside bound thereto and the outer, gastroresistant coating.

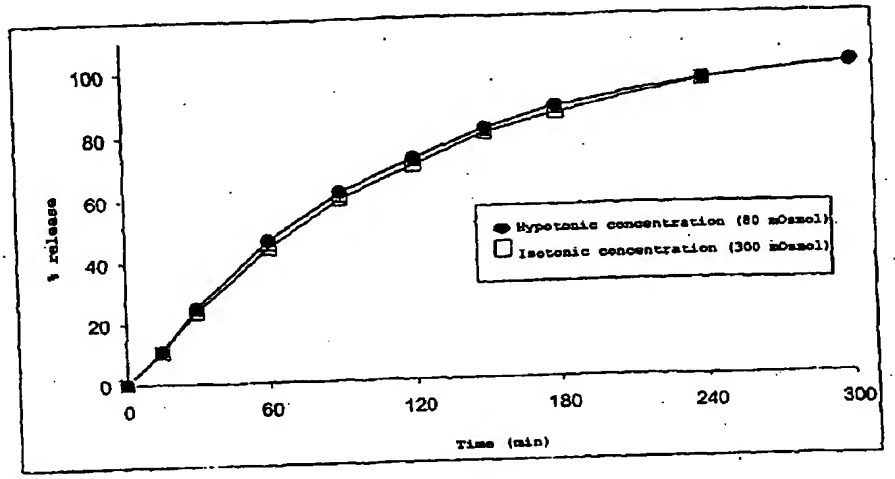

Fig. 5

These results show that the release of the active from the pellet is unaffected by the osmotic conditions in the release medium. Again, referencing Example 1 and FIG. 2 above, the conclusion that is drawn from these experiments is that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

Example 6, uses the same outer, gastro-resistant coating (Eudragit® L30 D-55) as in Example 5 but instead of a methacrylate polymer within the defined parameters of the claims

(e.g., Eudragit® NE30D), Example 6 uses Eudragit® Rl 30D (not within the defined parameters in the claims). As shown in the Table on page 34, the inner coating included only this RL30D material, the remaining ingredients are for the outer gastro-resistant coating. The results of this experiment are shown in FIG. 6.

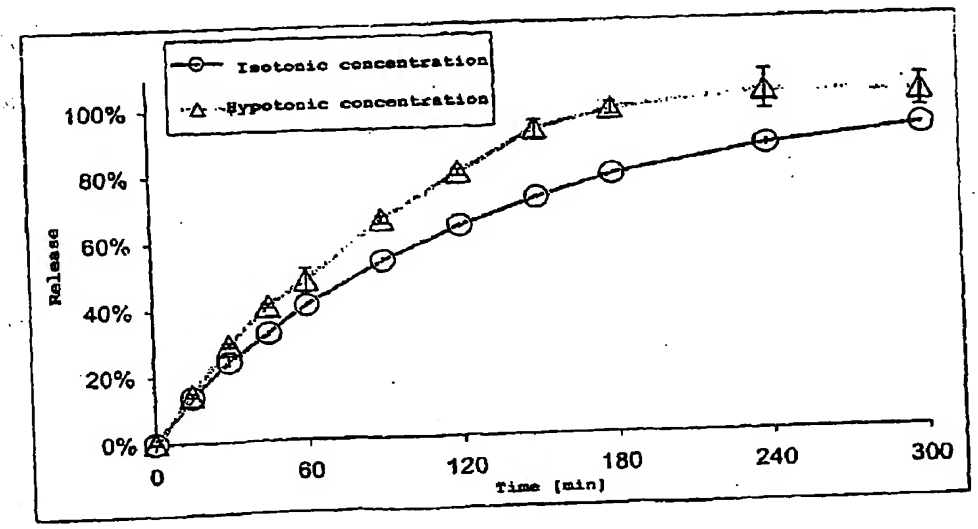

Fig. 6

These results show that the replacement of Eudragit® NE30D with Eudragit® RL30D as the inner coat to which the active is bound had differential release depending on the osmotic conditions of the release medium. Taken together, Examples 1, 5 and 6 as well as FIGs 2, 5 and 6 demonstrate that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

The art cited in the rejections do not teach the selection and arrangement of polymers with the active substance as claimed and certainly do not provide a reasonable expectation for the release criteria defined in the claims. Therefore, the rejections are unsustainable and should be reversed.

II. FIRST GROUND OF REJECTION

In the Office Action, the Examiner has maintained the rejections in view of Ulmius (US 5,643,602) with Beckert et al (WO 01/68058).

Ulmius describes a multilayer drug delivery unit (see col. 5, lines 3-26) including any number of polymers, including Eudragit®-type polymers (see also the Examples). Col. 5 of Ulmius describes a first layer including many different types of polymers, including Eudragit® type polymers but none of the Examples in Ulmius describe polymers in the inner coat (or layer) that includes a polymer like that which is claimed). While the Examples use some of those Eudragit® polymers as the outer layer, the Examiner has determined that it would have been obvious to use any one of the Eudragit® polymers as an inner (or first) layer replacing the ethylcellulose (Aquacoat ECD30 is an aqueous dispersion of ethylcellulose[1]) as actually used by Ulmius. Beckert is cited for further evidence of actives and additional disclosure pertaining to multi-layer drug forms (see page 8 of the Official Action mailed April 16, 2008).

First, there is nothing in Ulmius which provides the necessary direction to specifically select the type of methacrylate polymer as the inner coat to which the active is bound as defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted release of the active that was not affected by the ionic strength of the dissolution medium (see Examples in the application and the discussion above) could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

These results presented in the specification show that the replacement of Eudragit® NE30D with Eudragit® RL30D as the inner coat to which the active is bound had differential

[1] See, e.g., www.fmcbiopolymer.com/pharmaceutical/Products/Aquacoat.

release depending on the osmotic conditions of the release medium. Taken together, Examples 1, 5 and 6 as well as FIGs 2, 5 and 6 demonstrate that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

Also, on page 5 of the Official Action, the Examiner noted that there were differences between the formulations of Examples 5 and 6 that may have contributed to the effect observed by the inventors and to which Appellants have relied upon in rebutting the obviousness rejection previously. As should be apparent from the above-discussion, the effect that was observed was the result of the selection of specific type of methacrylate polymer as the inner coating with the active bound thereto. The differences in the outer-coating are for the purpose of delaying release until a certain point in the gastrointestinal track but, again referencing FIG. 2 the effect was one due to the inner coating.

As explained in MPEP 2145: "An "obvious to try" rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. " [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740, 82 USPQ2d 1385, 1397 (2007).

However, as the evidence of record (in the specification) shows, reasonable prediction of success from the teachings of cited art are not present for the <u>percentage release of active substance</u> as defined in Claim 1 because the evidence shows that combinations within the teachings of Ulmius (see Example 6 of the present specification using an RL 30D inner coating) lead to compositions not meeting that definition. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): "To the extent an

art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

As is clear from the figures, when the composition as defined in the claims was tested, the release profile remained relatively unchanged in the different ionic conditions, which was not the case for the composition in Example 6. Such an effect could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

Still further, with respect to claims 13-16, the selection of the specific methacrylate polymer enabled the active to be provided in the inner coating without the aid of excipients such as plasticizers or release agents as is typically the case in such formulations (see pages 4-5 in the specification citing to WO 01/68767, also the cited art. This is not at all suggested by Ulmius and/or Beckert.

As the basis of the rejection is *prima facie* reasonable predictability and the evidence shows that this is not the case, it has not been established that the claims are obvious in view of the cited reference.

In addition to their showing that there is no *prima facie* case, Appellants have shown an unexpected improvement in terms of the hypotonic/isotonic robust dissolution behavior. While Appellants do not concede that a skilled person would chose Eudragit® NE for the inner matrix from Ulmius and combine it with the outer Eudragit® FS coating of Beckert but even if that combination was appropriate, one skilled in the art would never expect the "hypotonic/isotonic" effect as has been so clearly demonstrated for the claimed invention.

There is nothing in Ulmius and Beckert which provides the necessary direction to specifically select the type of methacrylate polymer defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted slow release of the

active that was not affected by the ionic strength of the dissolution medium (see Examples in the application) could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

Further, the Office continues to misapprehend the evidentiary effect of unexpected results. In it's understanding, if it believes that it has made a *prima facie* case, no results provided by the invention could possibly be unexpected because they flow naturally from following the suggestion of the prior art (page 2 of the Advisory Action of March 22, 2010). In essence, the Office fails to understand the role of rebuttal evidence.

As the Board is well aware, it is legal error for the Office to dismiss a showing of unexpected results as flowing from or inherent in the Office prior art construct (in this case, the combination of Beckert and Ulmius). As stated in In re Sullivan, 84 USPQ2d 1034 (Fed. Cir. 2007):

> It is well settled that the PTO "bears the initial burden of presenting a prima facie case of unpatentability.... However, when a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). Rebuttal evidence is "merely a showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). Evidence rebutting a prima face case of obviousness can include: "evidence of unexpected results," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007), evidence "that the prior art teaches away from the claimed invention in any material respect," *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003), and evidence of secondary considerations, such as commercial success and long-felt but unresolved needs, *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999). When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability"); *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983) ("If, however, a patent applicant presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.").

Rather than considering the present showing of unexpected results as rebuttal evidence to an alleged *prima facie* case, the Office has dismissed it and, in fact, has clearly

convinced itself that unexpected results cannot exist when it thinks the Office has made a *prima facie* case. This is clear legal error.

In addition to their showing that there is no *prima facie* case, Appellants have shown an unexpected improvement in terms of the hypotonic/isotonic robust dissolution behavior. One skilled in the art would never expect the "hypotonic/isotonic" effect as has been so clearly demonstrated for the claimed invention. The Office has put forth no reasoning that would support a conclusion that, *looking forward*, such an improvement would have been expected from the combination of Beckert and Ulmius. Rather, the Office looks backwards and concludes that because it is the Office's opinion that the references present a *prima facie* case any property, benefit, or characteristic of the invention Applicant wishes to discuss in rebuttal is meaningless. As the Office is aware, this is completely improper and, at best, is a classic case of requiring comparison of the results of the invention with the results of the invention. See MPEP 716.02(e) and *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966).

As noted above in In re Sullivan, another source of rebuttal evidence is "evidence 'that the prior art teaches away from the claimed invention in any material respect.'" In this case the Beckert teaches away from the present invention because the pharmaceutically active substance is placed onto the neutral core and not bound in the inner coating material as claimed. Beckert suggests to use an inner coating based on Eudragit® RS/RL which does not work as evidenced by the data presented in the specification. There is nothing said about the hypotonic/isotonic effect.

There is nothing in Ulmius and Beckert which provides the necessary direction to specifically select the type of methacrylate polymer defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted slow release of the

active that was not affected by the ionic strength of the dissolution medium (see Examples in the application) could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

As the basis of the rejection is *prima facie* reasonable predictability and the evidence shows that this is not the case, it has not been established that the claims are obvious in view of the cited reference. Further, the evidence rebuts any alleged *prima facie* case of obviousness, showing the improved results that the specification states would not have been reasonably predictable based on what is described in the cited art.

Reversal of the rejection is requested.

III. SECOND GROUND OF REJECTION

The rejection combining Beckert with Gang. The Examiner relies upon Ulmius for the same teachings as in the first ground of rejection and finds that Ulmius does not disclose the combination of Eudragit® NE30D with Eudragit® FS, and therefore relies on Gang. (See pages 7-8 of the Official Action).

Gang teaches a colon delivery system employing an NE 30D inter coating and a FS outer coating. *Gang et al.* use the active ingredient (theophylline) placed in the pellet core and not bound in the inner methacrylate copolymer coating layer as claimed. This results in time dependent release curves (*s. Gang, Fig. 1*) which are different from the release curves of the present invention. Time dependent means that at the same pH the different examples of *Gang et al.* start the release of the theophylline, depending on the coating thickness of the inner EUDRAGIT® NE layer, at different times but then in the same fast manner (delayed pulsed release). In contrast to this the release of the active ingredient (e.g., budesonide) in the present application is triggered either by the proportions of EUDRAGIT® NE/budesonide (Fig. 1) and, most important, as a function of the pH (Fig. 3) and not as a function of time. Thus, the claimed invention and *Gang et al.* differ in the position of the active ingredient within the pellet and also remarkably in the kind of release curves.

In the Advisory Action of February 22, 2010, the Examiner concluded that "the location of the active ingredient comes from the teachings of the primary reference (Ulmius)" and again holding that the unexpected results relied upon in the present case are naturally flowing from the prior art constructs.

However, again the Examiner fails to understand and properly apply the role of rebuttal evidence, as already established in the discussion pertaining to the Ulmius and Beckert rejection above and as is clear from the figures. When the composition as defined in the claims was tested, the release profile remained relatively unchanged in the different ionic

conditions, which was not the case for the composition in Example 6. Such an effect could not have been predicted based on what Ulmius and Gang described (see page 5, last ¶ of the present application).

As the basis of the rejection is *prima facie* reasonable predictability and the evidence shows that this is not the case, it has not been established that the claims are obvious in view of the cited reference. In addition to their showing that there is no *prima facie* case, Appellants have shown an unexpected improvement in terms of the hypotonic/isotonic robust dissolution behavior. While Appellants do not concede that a skilled person would chose Eudragit® NE for the inner matrix from Ulmius and combine it with the outer Eudragit® FS coating of Gang but even if that combination was appropriate, one skilled in the art would never expect the "hypotonic/isotonic" effect as has been so clearly demonstrated for the claimed invention.

There is nothing in Ulmius and Gang which provides the necessary direction to specifically select the type of methacrylate polymer defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted slow release of the active that was not affected by the ionic strength of the dissolution medium (see Examples in the application) could not have been predicted based on what Ulmius and/or Gang described (see page 5, last ¶ of the present application).

Reversal of the rejection is requested.

IV. CONCLUSION

For the reasons stated in this Brief, Appellants respectfully request that the Examiner's rejections be withdrawn with direction to allow all of the claims pending in this application and pass this case to issue.

Respectfully submitted,

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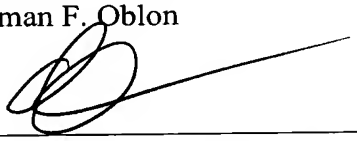
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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APPENDIX 1 (CLAIMS)

1. (rejected) A multilayer dosage form comprising

a) a neutral core,

b) an inner methacrylate copolymer coating comprising at least 90% by weight of (meth)acrylate monomers having neutral radicals, wherein the methacrylate copolymer has a minimum film-forming temperature as specified in DIN 53 787 not exceeding 30°C, and a pharmaceutically active substance bound to the methacrylate polymer, wherein the inner coating does not comprise plasticizer; and

c) an outer coating which comprises a (meth)acrylate copolymer which is composed of 10 to 30% by weight methyl methacrylate, 50 to 70% by weight methyl acrylate and 5 to 15% by weight methacrylic acid,

wherein the values for the percentage release of active substance in a hypotonic and an isotonic release medium based on phosphate buffer pH 6.8 do not differ from one another at any time in the period from 1 to 5 hours by more than 10%.

2. (rejected) The multilayer dosage form as claimed in claim 1, wherein the methacrylate copolymer of the inner coating is polymerized from 25-35% by weight methyl methacrylate, 75 to 65% by weight ethyl acrylate and, optionally, up to 10% by weight other vinylically polymerizable monomers, wherein the proportionate amounts add up to 100% by weight.

3. (rejected) The multilayer dosage form as claimed in claim 1, wherein the active substance/polymer ratio of the inner layer is from 20:1 to 1:20.

8. (rejected) The multilayer dosage form as claimed in claim 1, wherein said multilayer dosage form comprises an active substance from the active substance classes of aminosalicylates, of sulfonamides or of glucocorticoids.

9. (rejected) The multilayer dosage form as claimed in claim 8, wherein said multilayer dosage form comprises the active substance 5-aminosalicylic acid, olsalazine, sulfalazine, prednisone, prednisolone or budesonide.

13. (rejected) The multilayer dosage form as claimed in claim 1, wherein the inner coating comprises not more than 1% by weight of a release agent.

14. (rejected) The multilayer dosage form as claimed in claim 1, wherein the inner coating does not comprise release agents.

16. (rejected) The multilayer dosage form as claimed in claim 1, wherein the methacrylate copolymer comprise 65% by ethyl acrylate and 35% by weight methyl methacrylate.

APPENDIX II (EVIDENCE)

1. The present specification and accompanying figures, referenced in the arguments presented in this brief.

APPENDIX III (RELATED APPEALS AND INTERFERENCES)

None.